# RECHARGE YOUR PASSION FOR DRY EYE

# WHAT'S NEW AND WHAT'S COMING IN OSD TREATMENT

An overview of recent FDA approvals and potential new therapies.

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The New Year is always an exciting time, bringing forth new ideas, innovations, and technology. Let's take a moment to appreciate the recently approved therapies for patients with dry eye disease (DED), as well as other forms of ocular surface disease (OSD), and review those that may enter our treatment toolkit in the near future.

## RECENT APPROVALS

The FDA in February 2022 approved **cyclosporine ophthalmic emulsion 0.05%** (Mylan Pharmaceuticals), the generic form of Restasis (Allergan/AbbVie). This drug is an immunomodulator with an indication to increase tear production in patients with ocular inflammation due to keratoconjunctivitis sicca. It is a calcineurin inhibitor that works to downregulate the activation of T-cells in a preservative-free, anionic oil-in-water formulation made with castor oil.[1] The dosing is twice daily, but it can be used three to four times daily off label. As with any generic formulation, it's important to remember that the inactive ingredients can vary from the brand name drug, which can affect tolerability and efficacy.

Varenicline solution nasal spray (**Tyrvaya**, Viatris; formerly Oyster Point Pharma) garnered FDA approval in October 2021 for the treatment of the signs and symptoms of DED.[2] It is a highly selective cholinergic agonist designed to activate the trigeminal parasympathetic pathway, resulting in increased production of the basal tear film. It is dosed twice daily.

Santen Pharmaceutical received FDA approval in June 2021 for cyclosporine ophthalmic emulsion 0.1% (**Verkazia**) for the treatment of vernal keratoconjunctivitis (VKC). It employs a calcineurin inhibitor that downregulates the activation of T-cells using an improved penetration ability due to its positively charged cationic formulation. It is dosed four times daily and is the first and only immunomodulator to be approved for VKC.[3]

The FDA in April 2021 approved **OptiLight** (Lumenis) intense pulsed light therapy to treat DED due to meibomian gland dysfunction (MGD). OptiLight uses the company's patented Optimal Pulse Technology and user-centered design to allow more precise and targeted treatment. It reduces inflammatory mediators, improves tear break-up time, decreases osmolarity, alleviates abnormal blood vessels, restores meibomian glands, and decreases *Demodex* mites.[4] There is typically a series of four initial treatments spaced a few weeks apart.

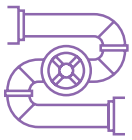
Loteprednol etabonate ophthalmic suspension 0.25% (**Eysuvis**, Alcon) is an ocular corticosteroid approved by the FDA in October 2020 for short-term use to treat DED and manage dry eye flare-ups.[5] This formulation

uses a proprietary technology, called Ampplify, with a mucus-penetrating particle to enhance ocular surface penetration through the mucous layer of the tear film. It is dosed four times daily for 2 weeks, although some practitioners use it longer off label.

## AN OFF-LABEL OPTION

Although not yet FDA approved, low-level light therapy (LLLT) or photobiomodulation is a common treatment approach used in dermatology and medical offices to repair damaged and compromised cells, while improving cellular function through its analgesic and antiinflammatory effects.[6] Its main use in DED is to improve the lacrimal and meibomian gland expression. A study by Park et al revealed that there have been slight improvements in tear break-up time, lid debris, lid swelling, lid telangiectasia, meibomian gland quality, and meibomian gland expressibility scores.[6]

Another off-label dry eye treatment that is well-known in dermatology is the use of radiofrequency (RF). RF uses a high-frequency electrical current to generate an optimal amount of heat to melt the thickened oil secretions inside the obstructed meibomian glands. The result is an enhanced lipid layer on the ocular surface to stabilize the tear film. It also helps to reduce ocular and adnexal inflammation. In addition, the consistent massage on the eyelid skin allows for an added benefit of simultaneous expression. There is usually a series of four treatments spaced every 2 to 4 weeks.[7]



## IN THE PIPELINE

Various novel therapies have reached major milestones on the road to FDA approval.

The FDA granted orphan drug designation for **BRM424** (Brim Biotechnology), a drug candidate for the treatment of neurotrophic keratitis. BRM424 will soon enter phase 2 clinical trials using the same active ingredient as BRM421, the company's leading candidate for DED that started phase 3 clinical trials in February 2023, with anticipated completion by end of the year or early 2024.[8] The active ingredient is a short peptide comprised of 29 amino acids derived from pigment epithelium-derived factor and is known to activate limbal stem cells to repair and regenerate the cornea, while also exhibiting antiinflammatory properties that can maintain the function of the goblet cells and meibomian glands to improve tear quality.[9] BRM421 completed the phase 2 trial and was shown to repair the cornea within 2 weeks and relieve symptoms within 8 days.[10] The data demonstrated clinically meaningful benefits and safety profiles. Brim Biotechnology has a third drug candidate in its pipeline, BRM423, which is targeted to treat severe corneal damage.[11]

> **AS IMPORTANT AS THESE THERAPIES ARE, WE CAN'T IGNORE THE SIGNIFICANCE OF SYSTEMIC, ENVIRONMENTAL, AND LIFESTYLE MODIFICATIONS IN SUPPORTING THE OCULAR SURFACE.**

Novaliq received new drug application (NDA) approval for its cyclosporine ophthalmic solution 0.1% (**CyclASol**) for treatment of DED. The drug is a first-of-its-kind antiinflammatory and immunomodulatory therapy that uses Novaliq's proprietary EyeSol technology to offer a multi-dose, water-free, preservative-free, small-sized drop. The technology allows a quicker onset of action, greater bioavailability and tolerability, and longer duration on the ocular surface. It has been studied in two key trials involving more than 1,000 patients at twice daily dosing for 12 weeks, which showed significant reduction in corneal fluorescein staining and significant improvement in tear production.[12,13] The anticipated Prescription Drug User Fee Act (PDUFA) target action date is June 8, 2023.

An investigational NDA has been accepted for **KPI-012** ophthalmic solution (Kala Pharmaceuticals) to treat persistent corneal epithelial defect. KPI-012 is a human mesenchymal stem cell secretome containing several human-derived growth factors, protease inhibitors, matrix proteins, and neurotrophic factors—all of which can help improve corneal healing.[14] It is in trials to assess the safety and efficacy of two doses applied topically four times daily for 56 days. Enrollment in the phase 2b clinical trial started in February 2023, with safety and efficacy data expected to be shared in the first quarter of 2024.[15] If the trial results are promising, Kala plans to submit this new treatment to the FDA for the biologics license application.

Kala is also targeting the potential development of KPI-012 for the treatment of partial limbal stem cell deficiency and the ocular

manifestations of moderate-to-severe Sjögren syndrome.[16]

Novaliq, in strategic cooperation with Bausch + Lomb, received NDA approval for perfluorohexyloctane ophthalmic solution 100% (NOV03) for the treatment of DED associated with MGD. It is distinct from the current antiinflammatory and immunomodulatory agents in that it is a preservative-free, water-free, nonsteroidal eye drop. This investigational therapy was studied in two pivotal trials involving nearly 600 patients each with four times daily dosing for 57 days.[17,18] NOV03 demonstrated statistically significant improvement for both primary and secondary endpoints and was well-tolerated with few adverse effects. If FDA-approved, NOV03 will be first in class to address excessive tear evaporation and tear film stabilization.[19] The anticipated PDUFA target action date is June 28, 2023.

Aldeyra Therapeutics recently announced the FDA's acceptance of its NDA for reproxalap ophthalmic solution 0.25% (Reproxalap), a reactive aldehyde species (RASP) inhibitor, for the treatment of DED via reducing ocular inflammation. RASP molecules are elevated in ocular and systemic inflammatory disease. There are a number of well-controlled, late-stage clinical trials that involved more than 2,000 participants. Studies show statistically significant and clinically relevant data with a rapid onset of action (within minutes) and lasting up to 12 weeks without any clinically relevant safety issues.[20-23] If approved, it would be the first drug in its class with this novel mechanism of action. The FDA assigned a PDUFA date of November 23, 2023.

Reproxalap ophthalmic solution 0.25% is also in phase 3 clinical trials for allergic conjunctivitis.[24,25]

The FDA in November accepted an NDA for lotilaner ophthalmic solution 0.25% (TP-03), Tarsus Pharmaceuticals' novel treatment of *Demodex* blepharitis.[26] The drug was studied in two pivotal trials involving 833 patients with twice daily dosing for 43 days, both of which successfully met their primary and secondary endpoints.[27] TP-03 showed significant improvement in signs and symptoms and was generally safe and well-tolerated with no serious adverse events. TP-03 works by paralyzing and eradicating *Demodex* mites by selectively inhibiting GABA-gated chloride channels.[27] If approved, it would become the first FDA approved treatment to set the standard of care for *Demodex* blepharitis. The anticipated PDUFA target action date for TP-03 is August 25, 2023. TP-03 is also in phase 2 trials for the treatment of MGD.[28]

## SIGNIFICANCE OF LIFESTYLE CHANGES

As important as these therapies are, we can't ignore the significance of systemic, environmental, and lifestyle modifications in supporting the ocular surface. Nutrition, hydration, exercise, sleep, stress management, and community support play an integral role not only in general health, but also in eye health. The ocular system is not an isolated system, but rather a reflection and manifestation of the complex human ecosystem. ■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